STUDY ON DRUG RELEASE CHARACTERISTICS THROUGH CONDUCTING POLYMER BASED COMPOSITE MATERIAL

Thesis on

"STUDY ON DRUG RELEASE CHARACTERISTICS THROUGH CONDUCTING POLYMER BASED COMPOSITE MATERIAL"

Submitted by

TITHI KUNDU

UNIVERSITY ROLL NO: 001710303003

EXAMINATIONS ROLL NO: M4BPE19004

REGISTRATION NO: 140623

SESSION: 2017-2019

MASTER'S IN BIOPROCESS ENGINEERING

PROJECT SUPERVISOR:

Prof. Kajari Kargupta

Department of Chemical Engineering

Jadavpur University, Kolkata

This project is submitted towards the completion of Master's in engineering degree in Bioprocess Engineering.

CERTIFICATION

This is to certify that Ms. Tithi Kundu, Final year Master's in Bioprocess Engineering examination student of Department of Chemical Engineering, Jadavpur University, and Examination Roll No: M4BPE19004*, Registration No.*140623 *of 2017-2019 , has completed the project work titled* ***"Study on drug release characteristics through conducting polymer based composite material"*** *under the guidance of* ***Prof. Kajari Kargupta*** *during her Master's curriculum. This work has not been reported earlier and can be approved for submission in partial fulfilment of the course work.*

……..

Prof. Debashis Roy

Head of Department and Professor

Chemical Engineering Department

Jadavpur University

……

Prof. Kajari Kargupta

Project Supervisor,

Professor,

Chemical Engineering Department,

Jadavpur University

Signature of Dean,

FET,

Jadavpur University.

Certificate of Approval

This thesis is hereby approved as a credible study of an engineering subject carried out and presented in a manner satisfactory to warrant its acceptance as a prerequisite to the degree for which it has been submitted. It is understood by this approval the undersigned do not necessarily endorse or approve any statement made, opinion expressed or conclusion drawn therein but approve the thesis only for the purpose for which it is submitted.

Signature of Examiners

Acknowledgement

I would like to take this opportunity to humbly express my heartfelt gratitude for the help, cooperation and inspiration that I have received from my departmental head Prof. Debashis Roy, teachers, friends and well-wishers during this course.

I feel honoured to express my profound regard and deep sense of gratitude to my Guide, Prof. Kajari Kargupta, for allowing me to do my work in this exciting field. She has been the person to instil in me a sense of commitment, dedication and optimism. I am highly obliged to my lab mates for their excellent guidance, endless encouragement, and unparalleled cooperation extended to me right from the time of onset of this colossal task till its successful completion.

I thank Mr Ajay Pradhan, technical assistant of Polymer Engineering Laboratory for his technical assistance that has helped me immensely to continue this work during M.E. course.

And finally, I remain indebted to my mentor/friend Dr Paramita Das, who has guided me right from the scratch to finish for this thesis. Her scolding and praises are the reason that this work shaped out in this manner.

TITHI KUNDU

CONTENTS

ABSTRACT

Conducting polymer (CP) and hydrogel based controlled drug delivery system, responsive to pH and external electrical signaling is developed, characterized and tested. In this system, polypyrrole (CP) is incorporated within a polyacrylamide hydrogel network along with the anti-psychotic drug Chlorpromazine. PPy based drug delivery systems have the potential to offer unique benefits to patients where the release rate of the drug can be tailored to meet the dosing requirements as per patient's compliance.

Polypyrrole (CP) and polyacrylamide-sodium alginate hydrogel are synthesized and characterized using SEM, TGA/DTA, FTIR, XRD; Point of zero charge, water retention and pH responsive swelling characteristics are determined for the synthesized hydrogel and CP. Drug release by diffusion as well as by electrical stimulus at different pH conditions, are investigated. The release profiles are characterized using known mathematical models for drug release. This system has the potential for sustained release of the drug.

Polyacrylamide-sodium alginate hydrogel exhibits pH responsive maximum drug release at slightly alkaline (pH 7.4) environment. Use of PPy along with polyacrylamide-sodium alginate hydrogel enables one to enhance the drug release rate upon electrical stimulation especially in the acidic pH environment. Also, cyclic voltammetry induced zero order linear release characteristics are achieved using Conducting polymer PPy. Without any electric stimuli, drug release through Polyacrylamide-sodium alginate hydrogel follows diffusive mechanism and release characteristics are best fitted with Higuchi model.

Keywords: polypyrrole, drug, hydrogel, controlled drug delivery, electrical stimulus, pH responsive

LIST OF FIGURES

Chapter 1

Introduction to controlled Drug delivery systems

1. INTRODUCTION:

Controlled drug delivery systems are dosage forms (tablet, capsules, injection, implant) designed to release therapeutic agents at a predetermined rate to a specific target in the body. The primary method of accomplishing this controlled release has been by incorporating the therapeutic agents within biocompatible polymers. In recent years, polyacrylamide hydrogels have been used for several applications like artificial implants, dialysis membrane, and controlled drug release system [1].

The circulating blood in our body is separated from the brain and extracellular fluid in the central nervous system by the presence of a semipermeable barrier called the blood-brain barrier. This barrier is made up of endothelial cells in tight junctions. Such tight junction selectively allows the passage of only small molecules. Thus in cases where therapeutic agents are targeted to specific regions of the brain, the blood-brain barrier hinders the delivery of drugs/antibodies in required dosage. Conventional dosage forms fail to produce the desired therapeutic effect in such areas. One of the proposed ways to deliver drug behind the blood-brain barrier is by using intracerebral implant [2].

Advantages of controlled drug delivery methods:

The following advantages of a controlled drug release system makes this a very sought after research arena.

- Prolonged therapeutic effect can be achieved.
- Predictability of the drug release profile rate of drug delivery at a pre-determined rate both locally and systematically.
- Improved patient convenience
- Reduction in fluctuation in steady state level
- Increased safety margin of high potency drugs
- Overall reduction in total healthcare cost. [3]

Types of Drug Release Systems: [4]

A. Rate programmed drug delivery system- The drug is released at a programmed release rate. They are further subdivided into subclasses-

1. Dissolution drug delivery system- It is designed such that the drug or the matrix/ membrane has slow dissolution rate.

2. Diffusion drug delivery system- Consists of porous matrix/membrane controlled system

3. Erosion drug delivery system- Drug is released via surface erosion.

B. Stimuli activated drug delivery system-

1. Activation by physical process- like temperature, electric field etc. [5]

2. Activation by chemical process

3. Activation by biological system

1.2. Diffusion controlled Drug Delivery Systems

Most drugs are transported across membrane by passive diffusion. The transport stream Q depends on the diffusion constant of drug in lipid material D, the surface area A, the partition coefficient K, the membrane thickness "h" and the concentration C_0 and C_i on both sides of the membrane.

$$Q = D \times A \times K\,(C_0 - C_i)/h \qquad \text{---------- (1.1)}$$

Diffusion can be defined as a process by which molecules transfer spontaneously from one region of higher concentration to another with relatively lower concentration in such a way as to establish thermodynamic equilibrium. The driving force for diffusion is the concentration gradient. The migrating molecules, diffusants migrate across the diffusional barrier (diffusion matrix or membrane) through the medium. The equations were put forth by Fick as an analogy to the heat-conduction equation developed by Fourier. The theory of diffusion hypothesizes that the flux J or rate of diffusion (amount Qt in time t) through a unit area of a diffusional barrier section is proportional to the concentration gradient normal to the section. This is Fick's first law, with the proportionality constant D termed diffusivity or diffusion coefficient.

1.3 Drug release from electric current sensitive polymers: Stimuli sensitive hydrogels have the potential for application in modulated drug delivery because these polymers not only respond to external stimuli, but also can be fabricated to control the release rate of drugs [6]. External signals that have been used in pulsatile drug release system are ultrasound, temperature, magnetic field, photo irradiation and electric field. From a practical point of view, electric signals would be the most convenient. [7]

Electrical signals are easy to generate and control. Electrical stimuli have been successfully utilized to trigger the release of molecules via conducting polymeric bulk materials or implantable electronic delivery devices. Electric current sensitive hydrogels are usually made of polyelectrolytes and an insoluble, but swellable, polymer network which carries ions. [8]

In electricity driven release systems, the main constituents are a polymeric network (hydrogel) to hold the drug, a bio-compatible conducting polymer (to conduct electricity) and a dopant (drug).

Conducting polymers (CPs) have attracted much interest as suitable biological compatible polymer matrix in which a number of drugs and enzymes can be incorporated (loaded) by ways of doping and hence have found use in enhancing the stability, speed and sensitivity of various biomedical devices. Moreover, CPs are inexpensive, easy to synthesize and versatile because their properties can be readily modulated by

(i) surface functionalization methods and (ii) the use of a wide range of molecules that can be entrapped as dopants. This ability of the CP to induce various cellular mechanisms widens its applications in medical fields and bioengineering.

Conducting polymers have the ability to undergo reversible red-ox reaction under the stimulus of an electric potential. The doped polymer film can be electrically switched between the oxidized state and the reduced state [9]. The red-ox reaction involves subsequent charging and discharging of the CP and is further accompanied by the movement of hydrated dopant ions in and out of the bulk. Utilizing these features, research have been made to design release systems in which conducting polymers can be loaded with chemical substances (drug, growth factors, enzymes etc.) and the loaded dopants can be released in response to external electrical signaling. Polypyrrole (PPy) and its derivatives are among the most widely used conducting polymers [10] in biomedical applications due to their bio compatibility and customizability. [11-16]. Miller et

al. [12] observed that glutamate and dopamine can be released from a PPy membrane using potential control. Pyo et al. [13] have demonstrated that adenosine 5'-triphosphate (ATP) can be released from a polymer membrane in a controllable manner. A composite PPy film was used by Hepel and Mahdavi [14] for the controlled release of cationic drug Chlorpromazine.

From the chemical structure of a polypyrrole molecule, it is seen that it consists of a five- carbon pyrrole ring attached to amine group. The structure is resonance stabilized because of π-electrons. 'Hoping mechanism' of these electrons in polypyrrole is responsible for conducting electricity. Upon successful doping of the polypyrrole structure, the forbidden band between the valence band and the conduction band is substantially reduced giving rise to increased electrical conductivity. Thus, bio compatible agents which can act like dopants can be loaded in polypyrrole for efficient therapeutic outcome.

Polymers as biomaterial for delivery systems

A range of materials have been utilized to control the release of drugs and other bio-active agents. Only biopolymers can be used for such medical purpose.

To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of impurities. Some of the materials that are currently being used for controlled drug delivery include

• Poly(2-hydroxy ethyl methacrylate), poly(N-vinyl pyrrolidone), poly(methyl methacrylate), poly(vinyl alcohol), poly(acrylic acid), polyacrylamide, poly(ethylene glycol), poly(meth acrylic acid).

In recent studies, a blend of CP-hydrogel has been the chosen for drug release and delivery research [15]. The combination of the swelling properties of hydrogels [16] and the conductivity of conducting polymers [17, 18] provide many merits to a controlled drug release system. **Hydrogels** are polymer networks, capable of storing large amounts of water in their three-dimensional network without dissolving in water. The ability of hydrogel to store water is due to the presence of hydrophilic functional groups in their polymeric backbone while their crosslinks between network chains makes them resistant to dissolution.

Similied to naturally occurring tissue hydrogels are flexible in nature due to large water content making them highly bio compatible. [19]

Classification of Hydrogel According to Polymeric Composition:

a. Homopolymeric hydrogel- polymer constituting of single type monomer species. [20]
b. Copolymeric hydrogel- two or more different monomer species make up this type of polymer with atleast one monomer being hydrophilic. [21]
c. Multipolymer interpenetrating polymeric hydrogel- made of two independent cross-linked polymers. One of the polymer is cross-linked while the other is not.[22, 23]

Polyacrylamide is a co-polymer because it is made of acrylamide and acrylic acid. Polyacrylamide hydrogel is safe for delivering drugs owing to its biocompatible nature and hence does not cause toxicity at the tissue level. [24] The natural flexibility in living tissues is mimicked by polyacrylamide hydrogel by its ability to hold large amounts of water in its network. Presence of hydroxyl groups (-OH) in its polymeric backbone makes them highly hydrophilic and allows them to take up large amounts of water, forming hydrogel.

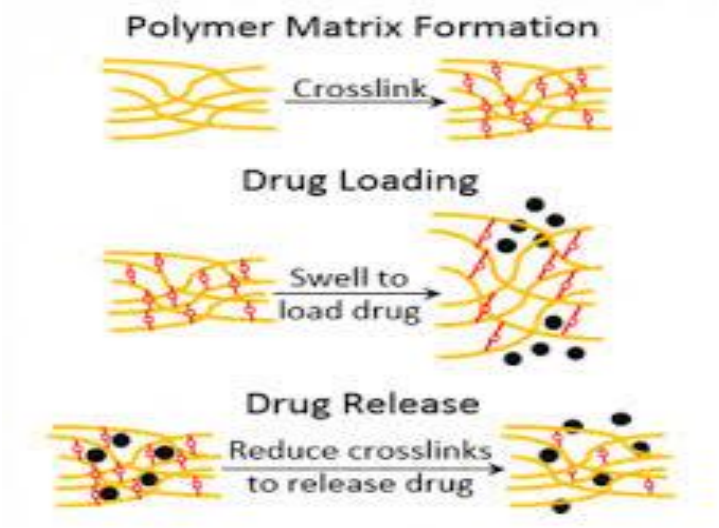


Fig. 1.1 Schematic of drug loading and release from polymer matrix

Source: http://amsdenlab.ca/category/research/

Desired biopharmaceutical characteristics of drug to qualify for control drug delivery: [25]

Molecular weight or size - Small molecules may pass through pores of a membrane by convective transport.

Solubility for all mechanisms of absorption- the drug must be present at the site of absorption in the form of solution.

Apparent partition coefficient (APC) - Drugs being absorbed by passive diffusion must have a certain minimal APC. The APC must also be applied for partition of the drug between CRDDS and the biological fluid.

1.4. Chlorpromazine as the chosen drug in a controlled delivery system.

Chlorpromazine is an anti-psychotic medication used primarily to treat psychotic disorders such as schizophrenia, bipolar disorder etc. It can be given by injection and oral intake. It acts as a dopamine antagonist [26]. Chlorpromazine being a mobile cationic molecule can move from the polymer during redox switching [27]. In pharmacokinetic terms, the bioavailability of chlorpromazine varies from 10-80% person to person when taken orally. The drug has a half-life of about 30hours and is excreted through urine (43-65% in 24hrs). Its high degree of lipophilicity allows it to be detected in urine even after 18months. It has a molar mass of 318.86g/mol (free base) and 355.33g/mol (hydrochloride). The chemical structure of chlorpromazine shows a –Cl group, which is released in aqueous solution thereby rendering the molecule positive charge overall.

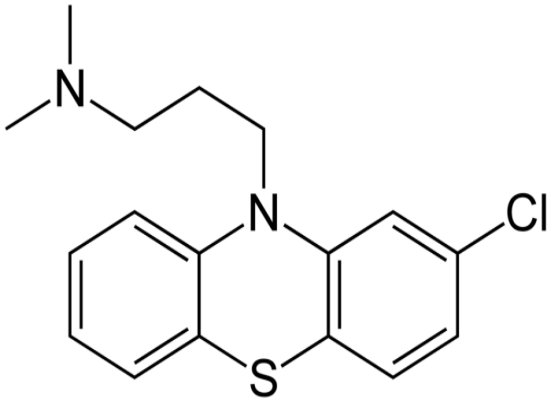


Fig1.2. Schematic of molecular structure of chlorpromazine.

1.5. Modeling Drug of Release profile

In the present work, some analytical models were used to study the mechanism of drug release of extended release by following models.

Zero order [28]

Drug dissolution from pharmaceutical dosage form that doesn't disaggregates and release the drug slowly can be represented by the following equation

$Q_0 - Q_t = K_0 t$ ----------1.2

Where,

Q_t =amount of drug released in time t

Q_0= initial amount of drug in solution

K_0 =zero order release constant

Application:

Pharmaceutical dosage forms following this profile release the same amount of drug per unit of time and it is ideal method of drug release in order to achieve prolonged pharmacological effect.

First order model [29]

In this model the decimal logarithm of amount remaining in the matrix VS time will be obtained. It indicates first order release and expressed by following equation

$\log Q_t = \log Q_e + (K_i . t/2.303)$ -----1.3

where,

Q_t = amount of drug released in time t

Q_e = initial amount of drug in solution

K_i = first order release constant

Higuchi model [30]

Higuchi developed several models to study the release of water soluble and low soluble drugs incorporated within solid matrices; mathematical equations were obtained for drug particles dispersed in a uniform matrix behaving as diffusion media. This model describes the drug release characteristics as a diffusion process based on Fick's law by using the formula

$$Q_t = KH\sqrt{t} \quad \text{------ (1.4)}$$

Where,

Q_t = amount of drug released in time t

KH=Higuchi Constant

√t =dependent square root of time

Application: Higuchi model can be used to describe the drug dissolution of several types of modified release dosage forms as in the case of transdermal systems and matrix tablets with where the drug has low solubility.

Hixson-Crowell model [31]

Hixson-Crowell recognized that the particle regular area is proportional to the cube root of its volume derived the following equation:

$$W_0^{1/3} - W_t^{1/3} = K_s t \quad \text{----- (1.5)}$$

Where,

W_0 = initial amount of drug in the pharmaceutical dosage form

W_t = remaining amount of drug pharmaceutical dosage form at time t

K_s = constant incorporating the surface volume relation.

Application: The model describes the release of dose from system where there is change in surface area and diameter of particle/tablet.

.

Chapter 2:

Literature Review

Authors name/Journal name/volume/year/page/Title	Drug used	Conclusion
M.Hepel,F.Mahdevi, Microchem.J.56(1997)54 "Application of the Electrochemical Quartz Crystal Microbalance for Electrochemically Controlled Binding and Release of Chlorpromazine from Conductive Polymer Matrix"	Chlorpromazine Used in the treatment of Schizophrenia,nausea,vomiting,chronic hiccups etc.	No leaching out of melanin incorporated during the polymerization process of pyrrole and no deterioration of such composite films were observed even after fifty potential cycling. [14]
Masayuki Yokoyama, Glenn S. Kwon, Teruo Okano, Yasuhisa Sakurai, Takashi Seto,f and Kazunori Kataoka. Bioconjugate Chem. 1992, 3, 295-301 295 "Preparation of Micelle-Forming Polymer-Drug Conjugates"	Adriamycin Used for slowing or stopping the growth of cancer cells.	Obtained conjugates showed higher water solubility irrespective of large amount of conjugated Adriamycin and formed micellar structures with a hydrophobic core and hydrophilic outer shell. [32]
Shasha Honga, Zengbo Li a, Chenzhong Li b, Chuan Donga, Shaomin Shuanga. Applied surface Science.Volume 427,PartB,(2018)1189-1198 "Cyclodextrin grafted polypyrrole magnetic nanocomposites toward the targeted delivery and controlled release of doxorubicin"	Doxorubicin Used in treatment of blood, bone, breast, ovaries, testicles, thyroid, head and neck, bladder, stomach and soft tissues, Hodgkin's disease, lung cancer, non-Hodgkin's lymphoma, Wilm's tumour and neuroblastoma.	Equilibrium at 5hr adsorption capacity reached 447 mg/g (pH 7.4 and a DOX concentration of 0.7 mg/mL), at pH 5.0, 27.0% of DOX were released in 24 h. [33]
Kyo¨sti Kontturi, Pa¨ivi Pentti, Go¨ran Sundholm * Journal of Electroanalytical Chemistry 453 (1998) 231–238 "Polypyrrole as a model membrane for drug delivery"	Salicylate Used as an analgesic and antipyretic drug	5% spontaneously released during 21 h into an aqueous solution of 0.1 M NaCl for all film thicknesses studied. [34]
Kashma Sharma a , Vijay Kumar a, * , Babulal Chaudhary b , B.S. Kaith c , Susheel Kalia d , H.C. Swart . Polymer Degradation and Stability 124(2016) 101-111 Application of biodegradable superabsorbent hydrogel composite based on Gum ghatti-co-poly(acrylic acid-aniline) for controlled drug delivery	Amoxicillin trihydrate Used in treating peptic ulcers.	104ppm initial release at 2hr interval in basic medium. [35]

Kyo¨sti Kontturi, Pa¨ivi Pentti, Go¨ran Sundholm * Journal of Electroanalytical Chemistry 453 (1998) 231–238 "Polypyrrole as a model membrane for drug delivery"	Tosylate Treatment of infections of the urinary tract, Gonorrhea, Otitis media and other conditions.	Drug could be released in a controllable way from the PPy membrane. [36]
Suparna Saha, Priyabrata Sarkar, Mrinmoy Sarkar, Biplab Giri Royal Society of Chemistry Advances 5, (2015) 27665 "Electroconductive smart polyacrylamide–polypyrrole (PAC–PPY) hydrogel: a device for controlled release of risperidone."	Risperidone Atypical anpsychotic used in the treatment of symptoms of bipolar disorder and schizophrenia	Drug release kinetics were conducted in 900 mL of 0.1 N HCl (pH 1.2) and 900 mL of phosphate buffer (pH 6.8 and pH 7.4) kept at thermostatically controlled temperatures of 37 C using a stirred apparatus run at 100 rpm. [37]
Richard Justin, Biqiong Chen. Carbohydrate polymers 103(2013)70-80 "Characterisation and drug release performance of biodegradablechitosan–graphene oxide nanocomposites."	Fluroscein sodium	Optimum combination of strong, efficient and fast delivery of drug was obtained for 45.6 wt% loaded sample. [38]

****

.

Chapter 3:

Aim and Objective

3.1. The main aim of this work is-

pH and electrical stimuli responsive controlled release of drug entrapped within a hybrid system of conducting polymer and hydrogel

3.2. The specific objectives of this work are-

1. Synthesis of conducting polymer Polypyrrole

2. Synthesis of Chlorpromazine (drug) loaded Polyacrylamide-Sodium alginate hydrogel

3. Synthesis of Chlorpromazine (drug) loaded Polypyrrole-Polyacrylamide-Sodium alginate hybrid system

3. Characterization of synthesized materials by PZC Analysis, Swelling Ratio, XRD, FTIR, SEM, TGA-DTA, Water retention.

4. Invitro drug release studies with and without external electrical signaling.

5. Fitting of different mathematical models with experimental release data and determination of drug release characteristics.

Chapter 4:

Experimental Work and Methodology

4.1. Synthesis:

4.1.1. Preparation of polypyrrole-

Polypyrrole is a type of organic polymer formed by pyrrole polymerization (oxidation). PPy is an insulator but its oxidized derivatives act as good electrical conductors. Conductivities range from 2-100 S/cm. Most commonly PPy is prepared by using ferric chloride in methanol.

$nC_4H_4NH + 2FeCl_3 \rightarrow (C_4H_4NH)_n + 2HCl + 2FeCl_2$

Preparing conductive forms of PPy:

Conductive forms of polypyrrole are prepared by the p-doping of the polymer.

$$(C_4H_4NH)_n + x\ FeCl_3 \rightarrow (C_4H_2NH)_nCl_x + x\ FeCl_2$$

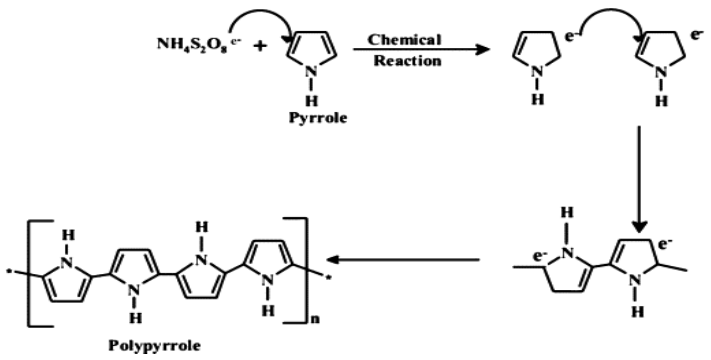


Fig4.1. Schematic showing synthesis of Polypyrrole from pyrrole.[39]

(a) (b)

Fig4.2. Synthesized polypyrrole (a) after synthesis and (b) after drying in vacuum oven

4.1.2. Synthesis of hydrogel-

Sodium alginate along with polyacrylamide forms hydrogel. Acrylamide mixed with bisacrylamide forms a cross-linked polymer network when the polymerizing agent, sodium disulfite and sodium peroxo disulfate (initiators) are added to a homogeneous solution of sodium alginate in double distilled water. TEMED (N,N,N,N'-tetramethylenediamine) catalyzes the polymerization reaction by promoting the production of free radicals from ammonium persulfate. This mixture was divided into two equal sections.

In one part of the mix, the conducting polymer (polypyrrole) along with the drug (chlorpromazine) was incorporated in this mixture while stirring (C1 synthesis), while the other half of the mix had only chlorpromazine without the conducting polymer (C3 synthesis). The beakers were covered with parafilm and further purged with nitrogen gas. The initiators were added equally to both the mixtures. Both the mixtures were poured into glass fusion tubes with platinum wires placed at the center of the tubes. The mixture was left to solidify in the tubes at room temperature. After solidification, the solid mix was taken out from the tubes and placed in oven for drying at 25^0C. The dried hydrogel was placed in desiccator for further experiments. The hydrogel with PPy incorporated inside was labeled as C1 and the polyacrylamide hydrogel without PPy was labeled as C3.

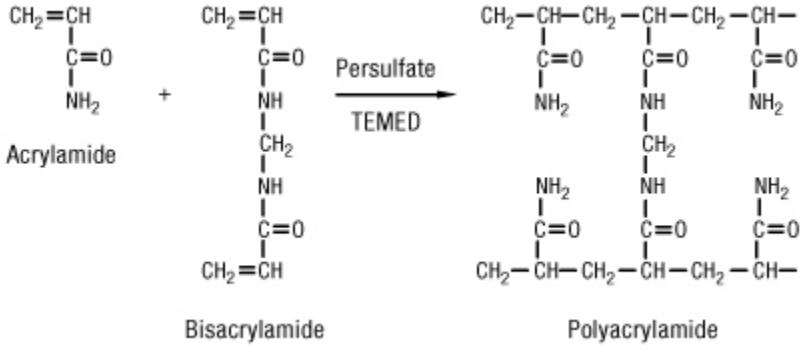


Fig4.3. Schematic representation of polyacrylamide synthesis. [40]

(a) (b)

Fig4.4. Polyacrylamide hydrogel synthesized in glass fusion tubes (a) PPy incorporated and (b) without the incorporation of PPy

4.2. CHARACTERIZATION:

4.2.1. X-Ray Diffraction-. The analyzed material is finely ground, homogenized, and average bulk composition is determined. XRD experiments were performed directly on the powdered samples using a Ultima III Diffractometer.

4.2.2. TGA- TGA of the hydrogel samples were carried out in a Mettler instrument in nitrogen atmosphere at the scanning rate of 10^0C/min in the temperature range of 25 to 600 ◦C.

4.2.3. FTIR- Fourier transform infrared (FTIR) spectra of the drug loaded and drug free samples were recorded on a FTIR spectrometer (Perkin Elmer, model-Spectrum-2, Singapore).

4.2.4. SEM**:** The morphology of the gels were observed by using SEM (Scanning electron Microscope, model no. S3400N, VP SEM, Type-II, made by Hitachi, Japan) with the accelerating voltage set to 15kV.

4.2.5. Swelling Ratio**:** Swelling characteristics of the hydrogels were studied in different pH (pH 1.5, 5, 7.4) at 37◦C. 50mg of hydrogel were immersed in each of the three 50 mL buffer solution. The swollen hydrogels were withdrawn from the solution at different time intervals (t) and weighed (W_t) after rubbing excess surface water with tissue paper. Swelling experiments were continued till the hydrogels reach their equilibrium swelling values (We). The swelling ratio (SR) was determined by using the following Eq.

$$SR\ (g/g) = \frac{W_t - W_d}{W_d} \qquad \text{------- (4.1)}$$

At swelling equilibrium W_t = We. Thus, Equilibrium swelling ratio (ESR) was obtained from the above Eq. by substituting W_t with We.

4.2.6. Water Retention**:** The hydrogel sample was first immersed in water till it reaches its equilibrium weight (We). Both of the hydrogel samples was then taken out and weighed at different time intervals (W_t) till constant weight at a temperature of 25 ◦C and relative humidity of 85%. Before each weight the wet gel sample was blotted with tissue paper to remove excess water. Water retention % (WR) of the gel sample was obtained as

$$WR\% = \frac{W_t}{W_e} \times 100 \qquad \text{---------- (4.2)}$$

4.2.7. PZC Analysis**:** PZC is the pH value at which there is no net electrical surface charge on a solid substance in an electrolyte solution. When the pH is lower than the pzc value, the adsorbent surface is positively charged (attracting anions). Conversely, above pzc the surface is negatively charged (attracting cations).

To determine the pzc value of our synthesized hydrogels, 40ml of buffer solutions ranging from pH 2 to pH 12 were taken and about 0.1g of both the hydrogels were added to each buffer solution and the flasks capped. The gel loaded solution was then kept for 48 h to reach equilibrium with occasional shaking. The pH of the supernatant liquid was measured (pH_f). The difference between this initial and final pH ($\delta pH = pH_i - pH_f$) was plotted against pH_i and the point of intersection of the curve at $\delta pH = 0$ gives the value of PZC for the hydrogel.

4.3. INVITRO DRUG RELEASE STUDIES:

The release of the anti-psychotic drug Chlorpromazine from the hydrogel samples were carried out with the help of both electrical signal and without the same.

4.3.1. **Drug release without using electrical signal-** Invitro drug release of chlorpromazine from the hydrogel samples was carried out at 35^0C using a magnetic stirrer at a rotation speed of 50rpm in 50ml buffer solution (pH 1.5,5.0,7.4) for 7-8hr. At time intervals of 30mins, 5ml of solution containing the released drug was withdrawn while simultaneously 5ml of fresh solution was added to keep the volume constant. The concentration of drug in the withdrawn solution was analyzed by UV/Vis spectrophotometer (Perkin Elmer Lambda 25, USA) at 253.5nm using a calibration curve constructed from a series of chlorpromazine solutions of known concentrations.

4.3.2. **Drug release by electrical stimulation-** The release of Chlorpromazine from polyacrylamide-polypyrrole hydrogel was triggered using cyclic voltammetry in an Autolab-PGSTAT302N where polypyrrole encapsulated polyacrylamide hydrogel (platinum wire inserted) was used as the working electrode, calomel as the reference electrode and platinum wire as the counter electrode. The voltage was swept from -0.8 to +1.2 V with a scan rate of 100mV/s. The experiment was carried for about 8hrs. The amount of Chlorpromazine released was quantified by measuring absorbance at 253.5nm in a UV/Vis spectrophotometer.

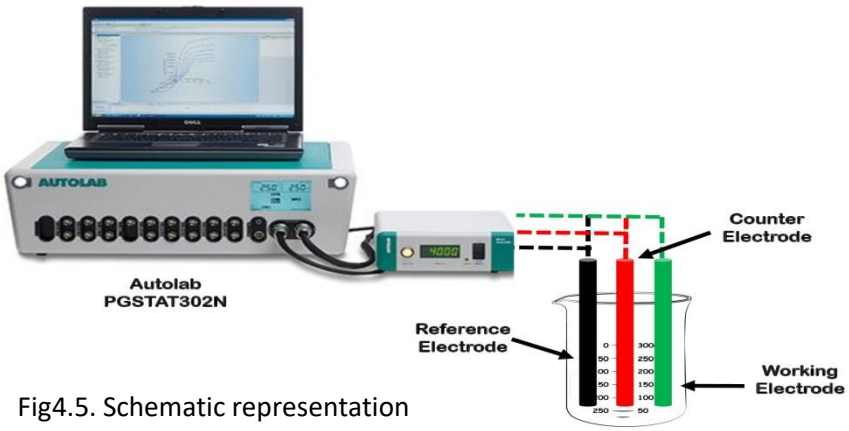


Fig4.5. Schematic representation of electrode setup for cyclic voltammetry

(a)

(b)

(c)

Fig4.6. Electrodes used in cyclic voltammetry (a) Calomel electrode as the reference (b) Platinum wire as counter electrode (c) Drug loaded hydrogel sample as working electrode.

Chapter 5

Experimental Results and Discussions

5.1: Characterization Study of the Hydrogel-

5.1.1: X-Ray Diffraction: The polyacrylamide hydrogel is formed by in situ polymerization of acrylamide in presence of sodium alginate and because of chemical bond formation due to the hydroxyl groups; crystallinity is reduced in its structure [41]. Sodium alginate shows crystalline peaks at 2θ of 19^0, 22^0 and 34^0 [42] whereas the hydrogels (C1 and C3) show only singular peak at 2θ of about 21.14^0 [43]. The hydrogels thus formed are amorphous in structure.

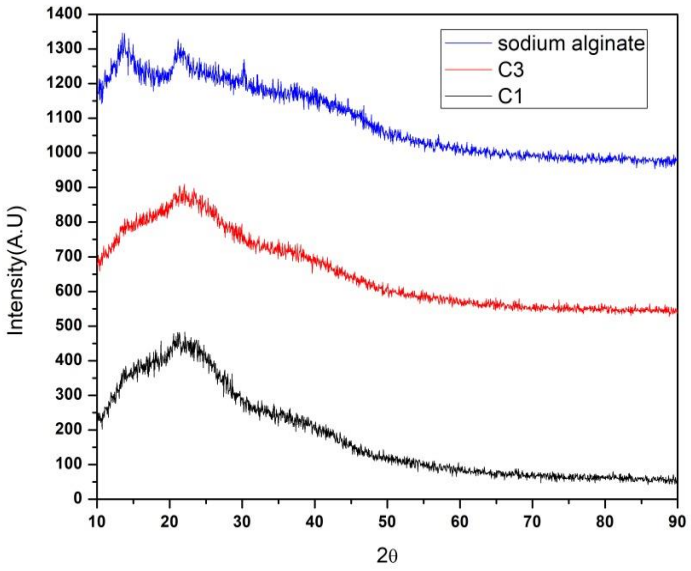
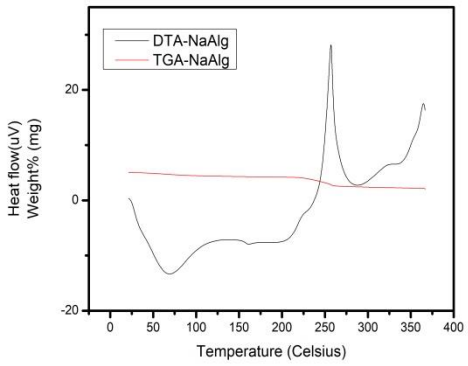


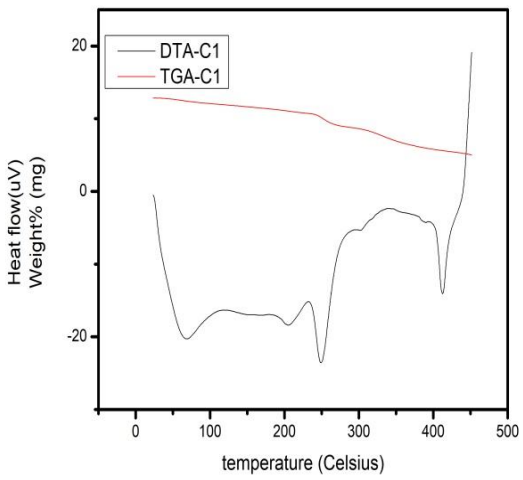
Fig5.1. XRD- analysis of sodium alginate, PPy incorporated hydrogel (C1) and Hydrogel without PPy (C3)

5.1.2: Differential thermal analysis and thermogravitametry analysis: The DTA and TGA of Sodium alginate, Hydrogel without PPy (C3) and hydrogel with incorporated PPy (C1) are shown in the fig. In terms of DTA, it is seen from (i) that Sodium Alginate shows peaks at around 87^0C owing to water loss [44]. Peak at 162^0C corresponds to its recrystallization [45] and at 228^0C and 257^0C corresponds to its degradation. Both the hydrogels, C1 and C3 show a similar kind of DTA profile with peak at 298^0C. From the TGA

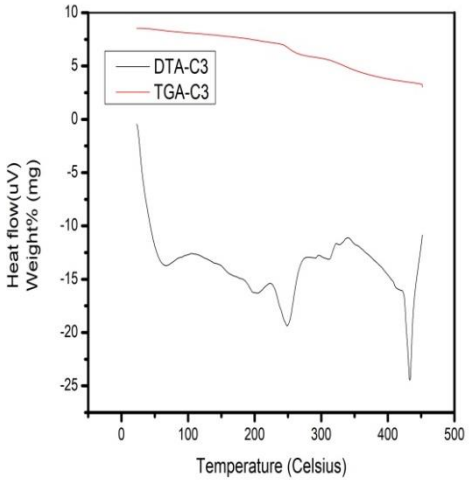
plots, we see that splitting of the main chain caused by thermal decomposition of the polymers has lead to weight loss in different temperature regions [46]. Maximum weight is lost at melting temperatures. Segments of mannuronic acid and glucuronic acid melts at 100-225^{0}C causing melting and degradation of sodium alginate. [47]



(a)



(b)



(c)

Fig 5.2. TGA-DTA plots of (a) Na-Alginate (b) PPy incorporated hydrogel and (c) Hydrogel without PPy

5.1.3. FTIR Spectroscopy: FTIR Spectra of drug loaded PPy incorporated hydrogel (C1D), Ppy incorporated polyacrylamide hydrogel (C1) and polyacrylamide/sodium alginate hydrogel without Ppy (C3) is shown in fig. Sample C3 shows characteristic peaks at 3432 cm^{-1} due to N-H stretching vibration and at 1632 cm^{-1} signifying the presence of C=O stretches.[48] Sample C1 shows peaks at 3420cm^{-1}, 2346cm^{-1} and 1615cm^{-1} showing N-H symmetric and asymmetric stretch, C≡N stretch and C=O stretch respectively [49]. Sample C1D gives absorbance peaks at 2675^{cm-1} and 1398^{cm-1} due to O-H stretch and C-N resp. [50]

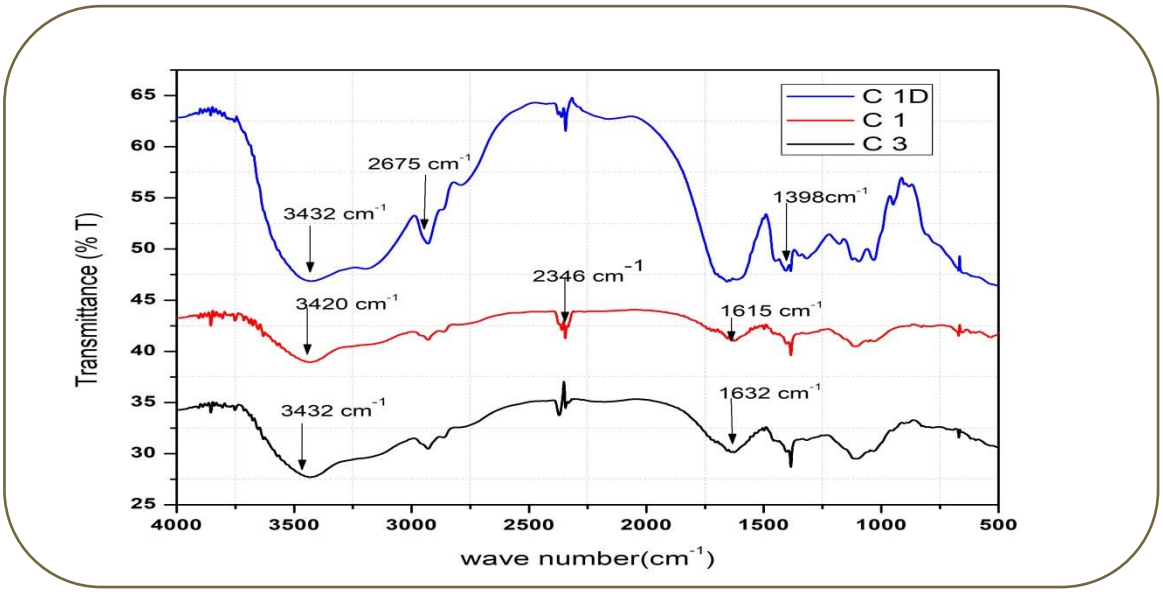
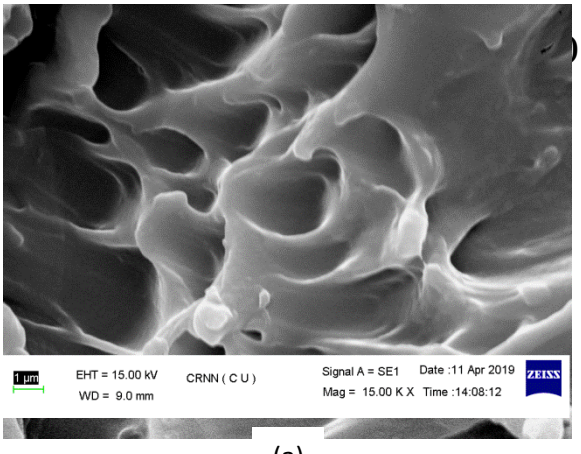
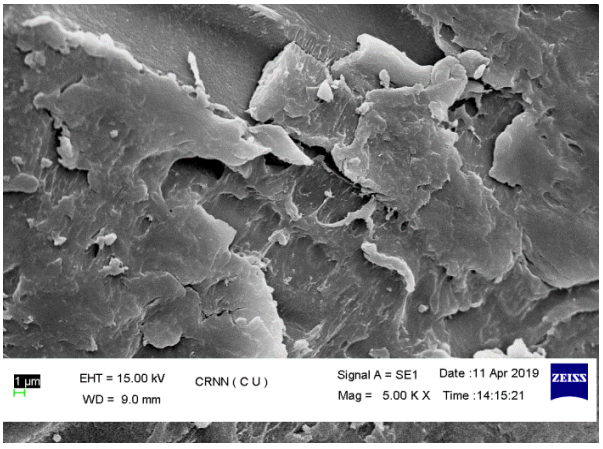


Fig5.3. FTIR Analysis of PPy incorporated hydrogel, drug loaded PPy incorporated Hydrogel and hydrogel without PPy.

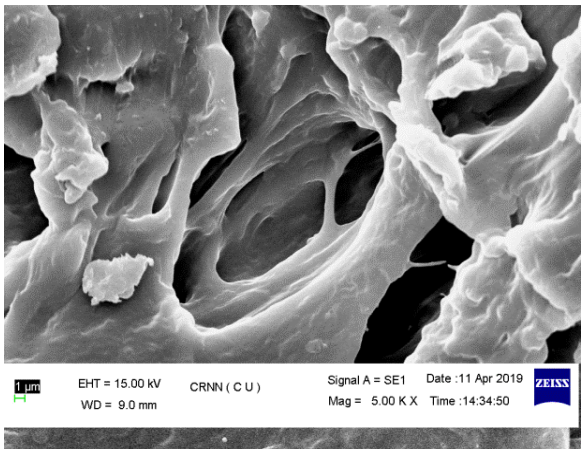
5.1.4. Scanning Electron Microscopy:

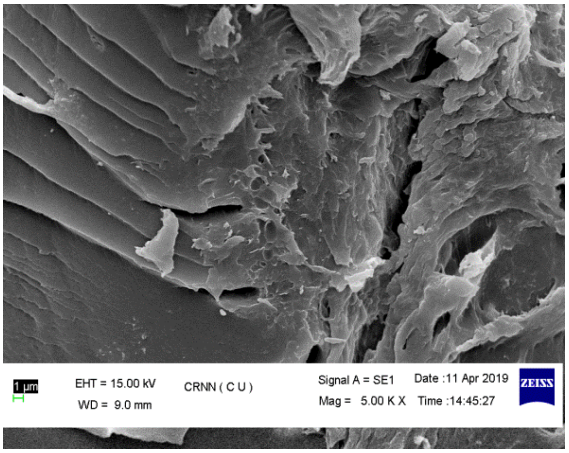


(a)



(b)



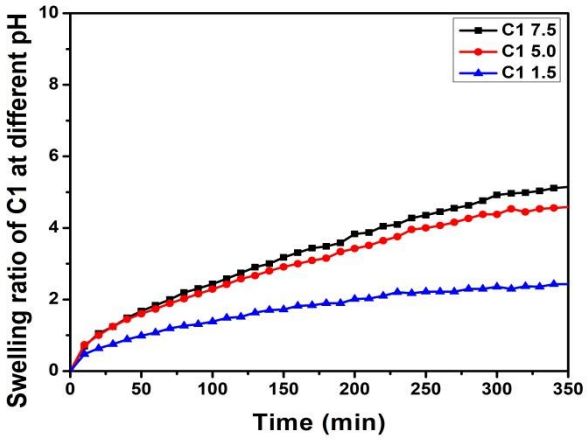


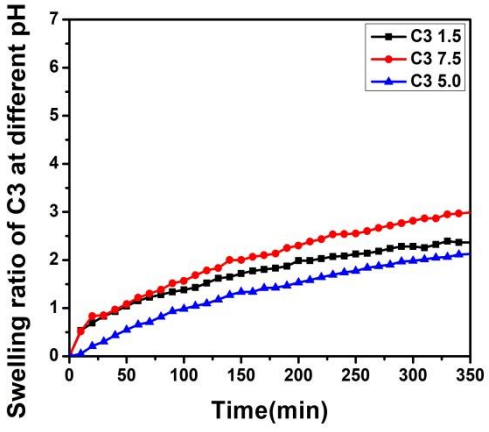
(c) (d)

Fig.5.4. SEM images of (a) PPy incorporated hydrogel (b) Drug loaded PPy incorporated hydrogel (c) Hydrogel without PPy and (d) Drug loaded in hydrogel without PPy.

The surface morphology of the samples clearly shows interconnected network and porous channels in (a) and (c) and that further drug can be incorporated (loaded) inside these. The porosity of the structure was greatly reduced due to chlorpromazine loading in the samples as shown in (b) and (d).

5.1.5. Swelling Ratio: Drug release properties of hydrogels strongly depend on its swelling characteristics. All of these swelling experiments were performed in buffer solutions of pH 1.5, 5.0 and 7.4. We see from the results that both the hydrogels (C1 and C3) swell most in pH 7.4.





(a) (b)

Fig5.5. Swelling characteristics of (a) PPy incorporated hydrogel C1 and (b) Hydrogel without PPy

5.1.6. Water Retention: Equilibrium weight, W_e of C1 and C3 are 11.745g and 15. 395g respectively. The constant weight, W_t of C1 and C3 are 7.833g and 10.361g respectively. Therefore, water retention of C1 and C3 as per the given formula is 66.69% and 67.3% respectively.

5.1.7. PZC Analysis: The difference between final pH (pHf) and initial pH (pHi) of the solution (pHf–pHi) is plotted against initial pHi for both of the hydrogels.. Depending on the pH of the solution hydrogel surfaces will be positively charged for pHi < pHPZC, negatively charged for pHi > pHPZC or neutral for pHi = pHPZC.

From Fig.5.6 it is observed that pHPZC of the PPy incorporated hydrogel in water is 3.5 which is 3.15 for hydrogel without PPy. Adsorption of the drug will be favored at solution pH > pHPZC.

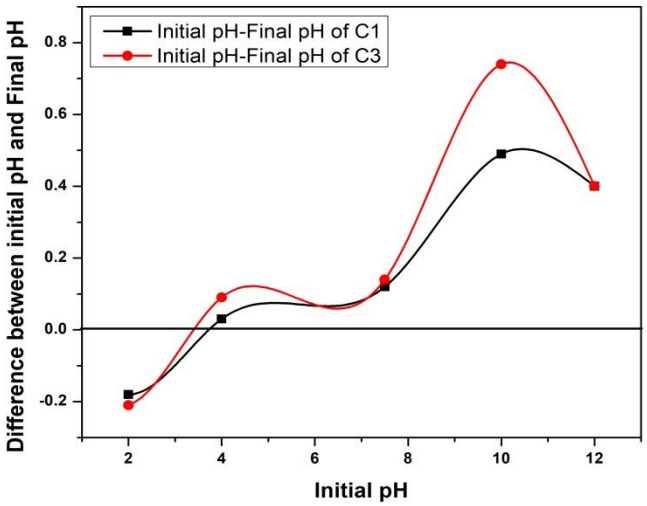


Fig5.6. PZC Analysis of PPy incorporated hydrogel (C1) and only hydrogel (C3)

Drug delivery system	PZC	Equilibrium Swelling Ratio at 7.4 pH	Equilibrium Swelling Ratio at 1.5 pH	Water Retention
C1(hydrogel with PPy)	3.5	8.96772	3.029412	66.69
C3 (Hydrogel)	3.15	6.31667	3.056338	67.3

5.2: Invitro Drug release study:

The drug release of chlorpromazine from both the hydrogels was performed in three different buffers of pH 1.5, 5.0, 7.5 under electrical stimulation and without it. The cumulative drug release concentration was obtained from a calibration curve made by obtaining absorbance of varying concentrations of aqueous solution of chlorpromazine spectroscopically.

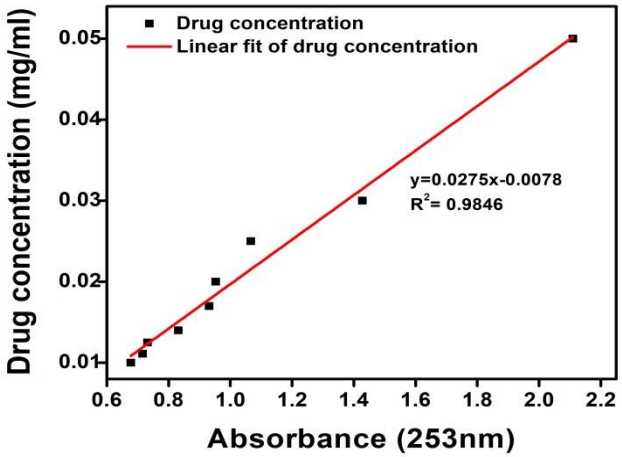


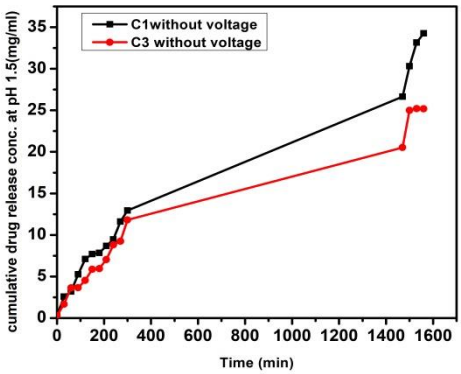
Fig. 5.7 Calibration curve of Chlorpromazine

Drug (released) Concentration based on buffer solution volume: $[Cd]_b$

Drug (remaining) % = $\{M_{loaded}-[Cd]_bV_b\}x100/M_{loaded}$

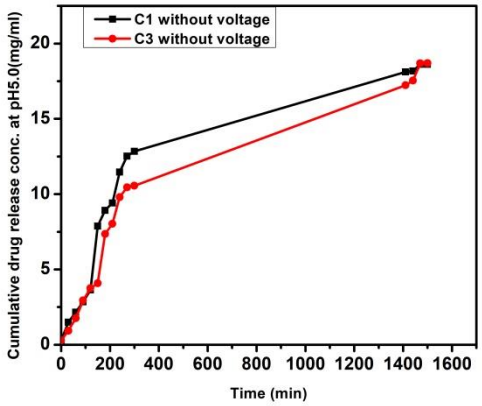
5.2.1: Drug release without electrical stimulation- Chlorpromazine release from both the hydrogels was conducted in 50ml of buffer of pH 1.5, 5.0, 7.5 using a stirred apparatus (magnetic stirrer) run at 100rpm in constant room temperature of about 35^0C. From these graphs (Fig5.8 a-c) we see that drug release is higher from the PPy incorporated hydrogel (C1) for the same time period. pH 7.5 gives the maximum chlorpromazine release for constant room temperature.

(i) Release at pH 1.5:



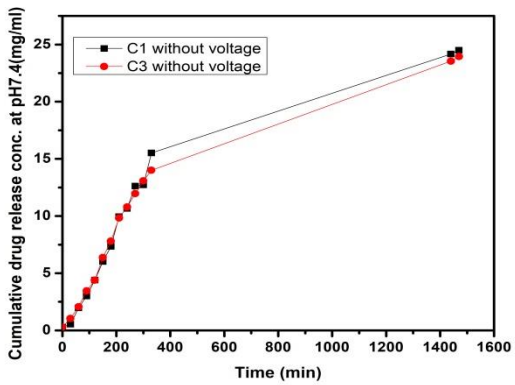
(a)

(ii) Release at pH5.0



(b)

(iii) Release at pH7.4



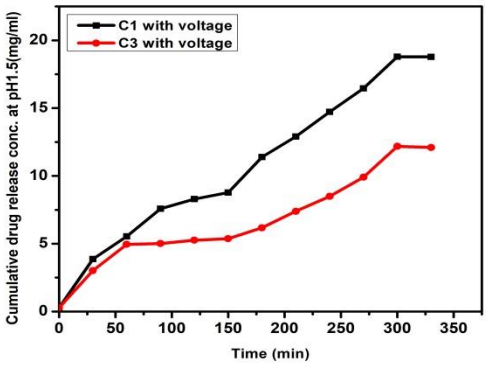
(c)

Fig5.8. Figure showing cumulative drug release without electrical stimulation at (a) pH1.5 (b) pH5.0 (c) pH7.4

The amount of drug released without electrical signaling is maximum in pH 1.5.

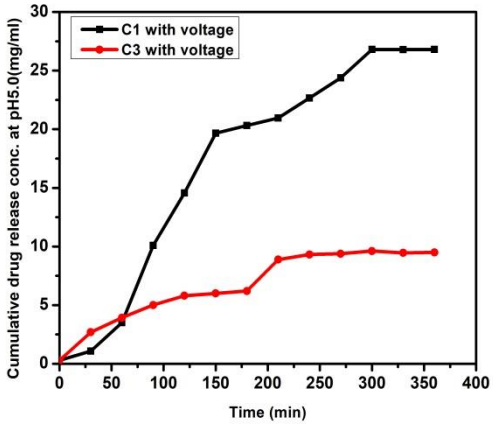
5.2.2: Drug release by electrical stimulation- The effect of potential on chlorpromazine release was ascertained by voltammetric study from -0.8V to +1.2V at the scan rate of 0.1V/s because the crossover points from anodic to cathodic currents has been found to lie within this window. The process was run for about 500cycles each time for about 3 times per sample. The released chlorpromazine (D1) was measured by UV absorbance at 235.5nm. The Characteristic Cyclic Voltammetry plots are shown below- (i) Release from C1 (ii) Release from C3

(i) Release at pH1.5



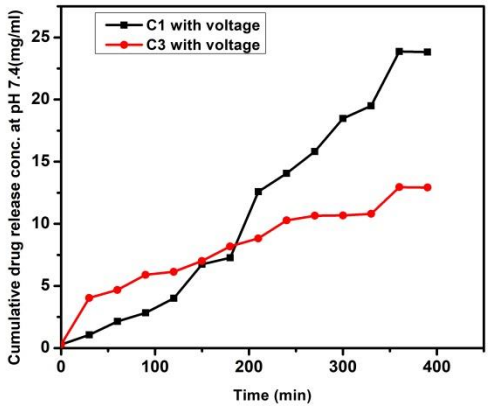
(a)

(ii) Release at pH5.0



(b)

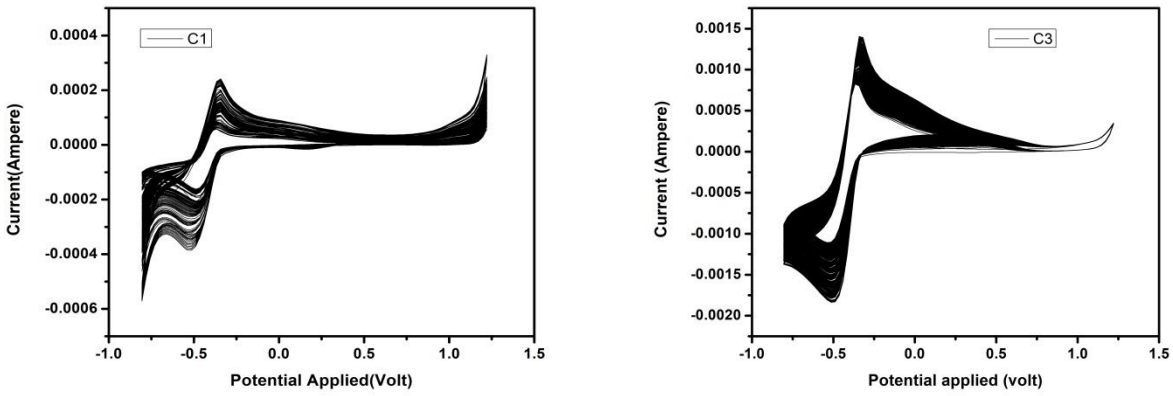
(iii) Release at pH7.4



(c)

Fig.5.9 Cumulative drug release under stimulation at (a) pH 1.5 (b) pH5.0 (c) pH7.4

In case of electrical stimulation, pH 7.4 shows maximum release of chlorpromazine.



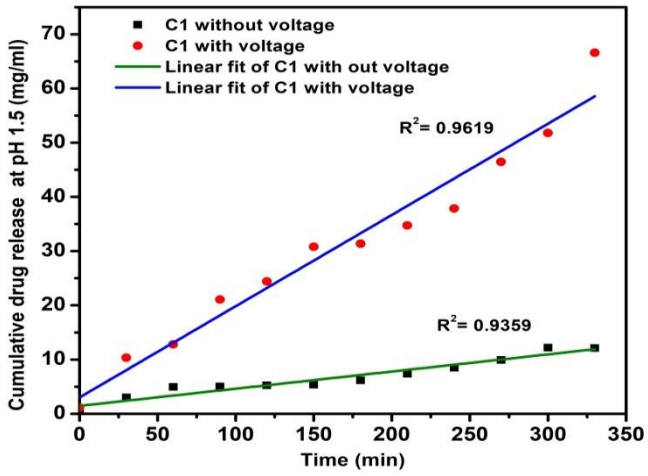
(a) (b)

Fig.5.10. Cyclic voltammetry plots of (a) PPy incorporated hydrogel (b) Hydrogel without PPY

5.3: Comparison between Chlorpromazine releases with and without the aid of external electrical signaling-

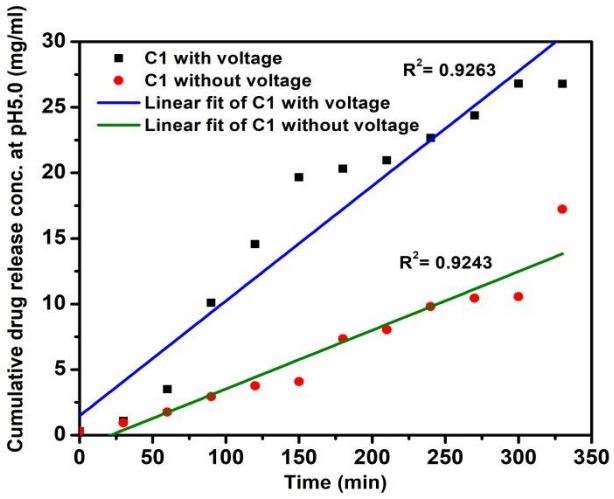
5.3.1. Comparative release from the PPy incorporated hydrogel (C1) –

(i) Release at pH 1.5



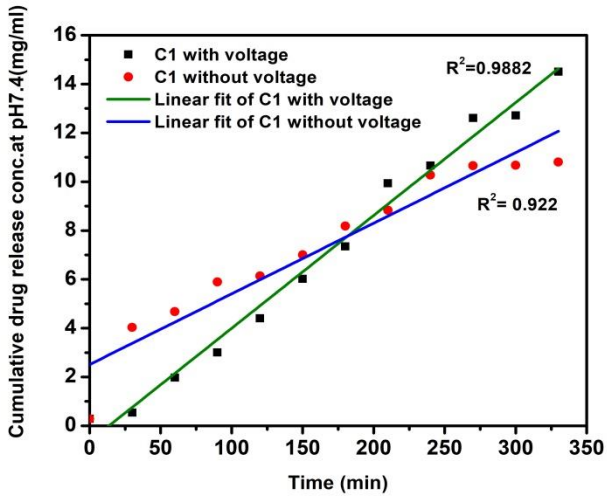
(a)

(ii) Release at pH 5.0



(b)

(ii) Release at pH7.5



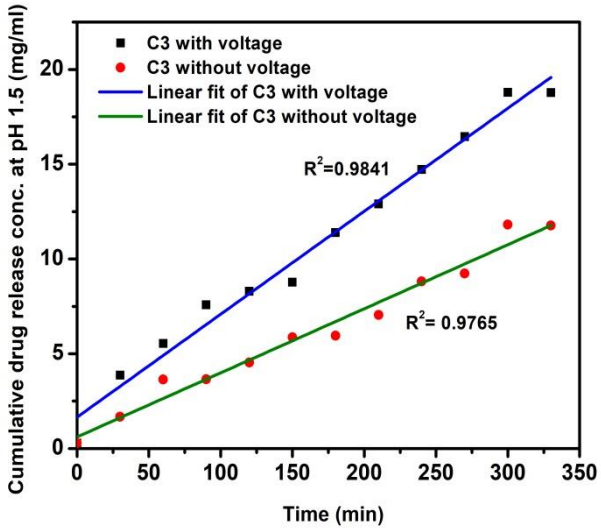
(c)

Fig5.11. Comparative analysis of drug release from PPy incorporated hydrogel with and without electrical signal (a) at pH1.5 (b) at pH5.0 and (c) at pH 7.4

Drug release with external electrical stimulation shows enhanced release rates; almost linear fit. The PPy in this hydrogel is responsible for increased reaction rates; 3 times at pH 1.5, approximately 2 times for pH 5.0 and for pH 7.4 slightly less than 2 times.

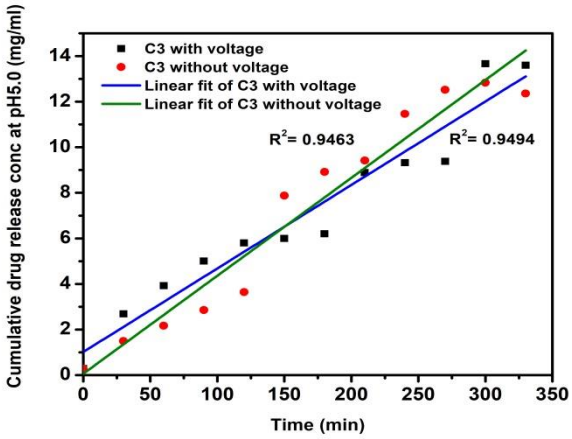
5.3.2. Comparative release from the hydrogel (C3)-

(i) Release at pH 1.5



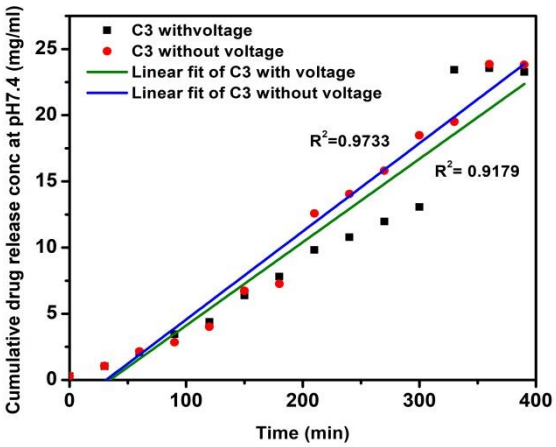
(a)

(ii**)**Release at pH 5.0



(b)

(iii)Release at pH7.4



(c)

Fig. 5.12 Comparative drug release form hydrogel without PPy at (a) pH1.5 (b) pH5.0 and (c) pH7.4

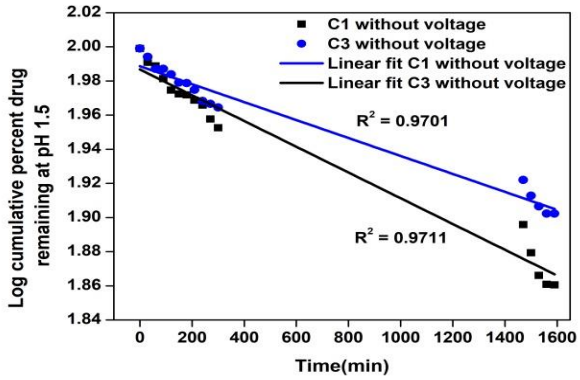
Due to absence of any conducting polymer, the rate of drug release (slope) remains almost unchanged on applying electrical stimulus for pH 5.0 and 7.4. But for pH 1.5, drug release is enhanced by almost 2 times upon electrical stimulation.

5.4: MATHEMATICAL MODELS FOR DRUG RELEASE:

5.4.1. **First Order Release**- This can be used to describe the drug dissolved in pharmaceutical dosage forms like those containing water soluble drugs in porous matrix. The data obtained are plotted as log cumulative percentage drug remaining versus time, which gives a straight line with slope = K/2.303, where K is the first order rate constant.

5.4.1.1. Release without external electrical signal-

(i) Release at pH1.5

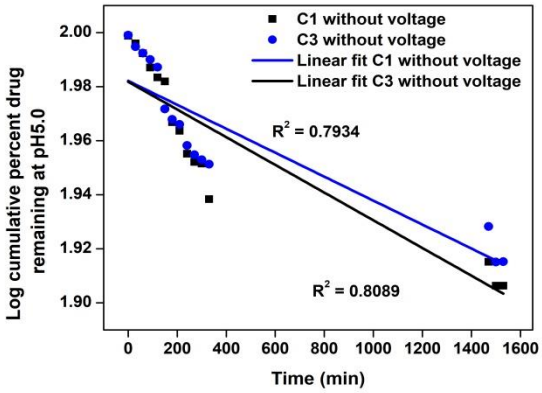


K_{C1} = -1.7064*10^{-04} min^{-1}

K_{C3} = -1.32*10^{-04} min^{-1}

(a)

(ii) Release at pH 5.0

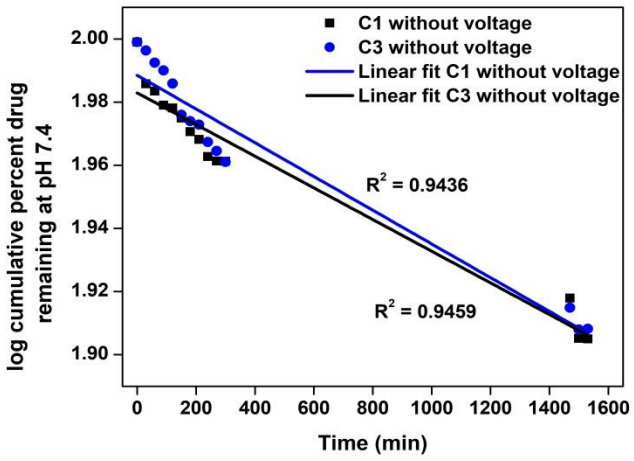


K_{C1} = -2.595964*10^{-04} min^{-1}

K_{C3} =-1.091846*10^{-04} min^{-1}

(b)

(iii) Release at pH 7.4



K_{C1}= -1.07822*10^{-04} min^{-1}

K_{C3}= -1.09844*10^{-4} min^{-1}

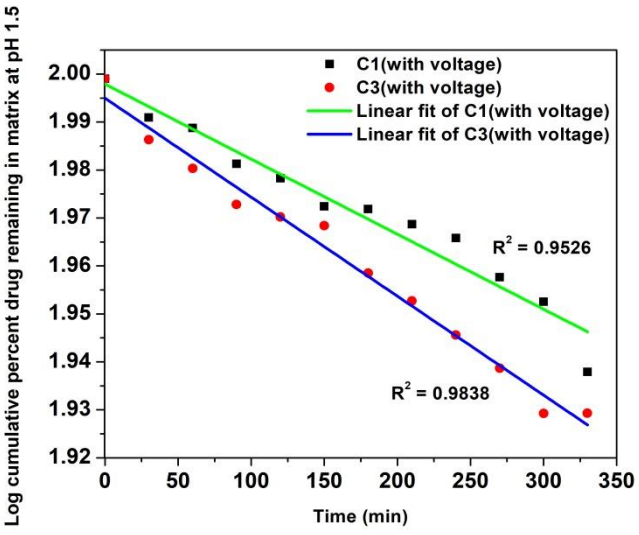
(c)

Fig.5.13. First order drug release without electrical signaling at (a) pH1.5 (b) pH5.0 (c) pH7.4

Without electrical signal, release at pH1.5 is most fitted for first order release closely followed by the release at pH 7.4

5.4.1.2. Release with the help of electrical signal-

(i) Release at pH 1.5

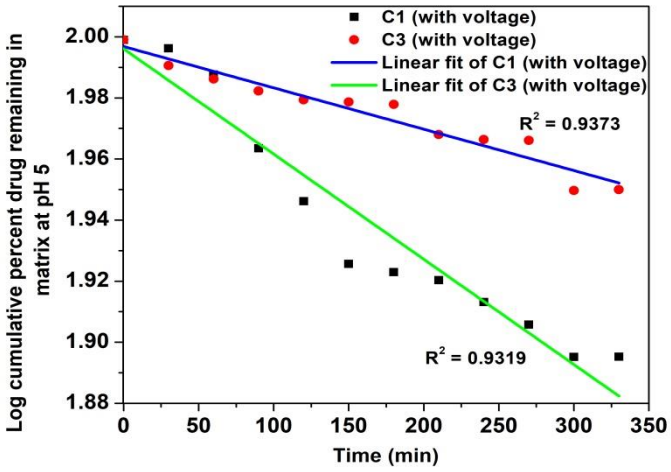


K_{C1}= -2.312*10^{-4} min^{-1}

K_{C3}= -3.11708*10^{-04} min^{-1}

(a)

(ii) Release at pH5.0

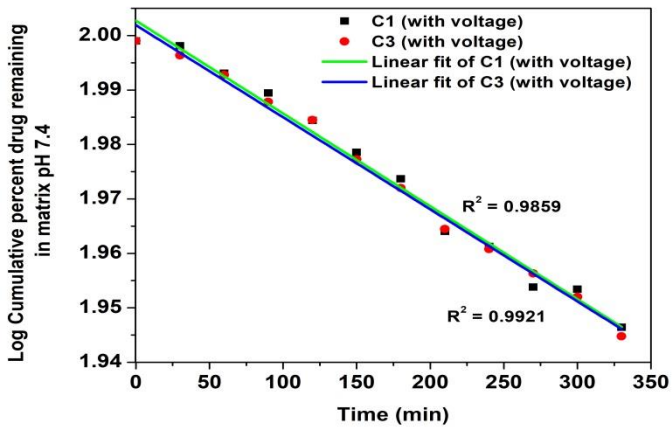


K_{C1}= -1.897528*$10^{-04}$$min^{-1}$

K_{C3}= - 2.1426*$10^{-04}$$min^{-1}$

(b)

(iii) Release at pH 7.4



K_{C1}= -9.8593*10-05 min^{-1}

K_{C3}= -1.0416*10-04min^{-1}

(c)

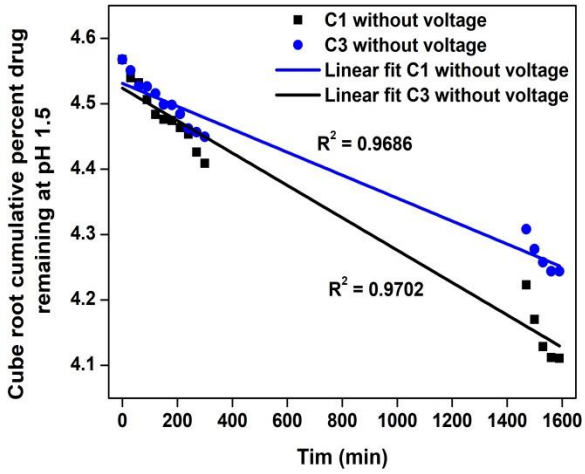
Fig.5.14. First order drug release with electrical signaling at (a)pH1.5 (b) pH5.0 (c) pH7.4

When aided by electrical signal, drug release at pH 7.4 follows first order kinetics, closely followed by release at pH 1.5

5.4.2. Hixson-Crowell Model- This model is used to describe drug release from a system prone to surface area change after the release. The plot is made between the cube root of drug percent remaining in matrix with time.

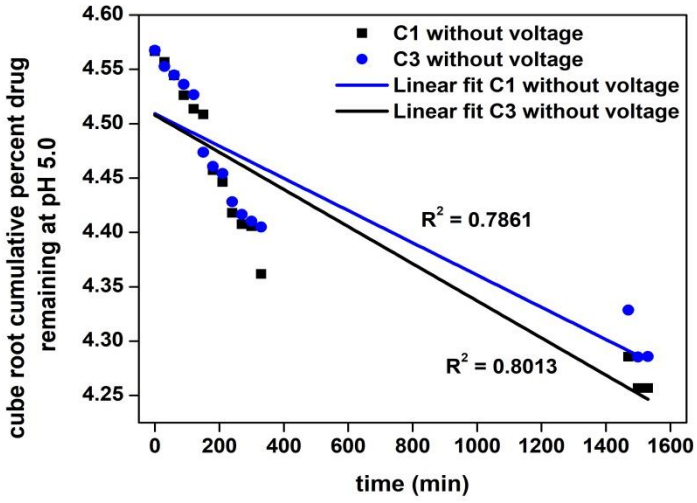
5.4.2.1. Drug release without voltage-

(i) Release at pH1.5



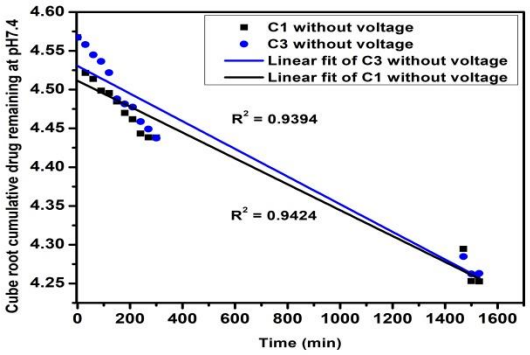
(a)

(ii) Release at pH 5.0



(b)

(iii) Release at pH7.4



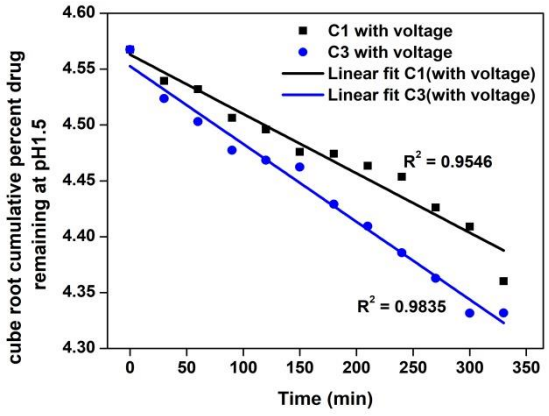
(c)

Fig.5.15. Hixson-Crowell drug release without electrical signaling at (a) pH1.5 (b) pH5.0 (c)pH7.4

From this plots, it is inferred that without electrical signal release at pH 1.5 is most fitted to this model.

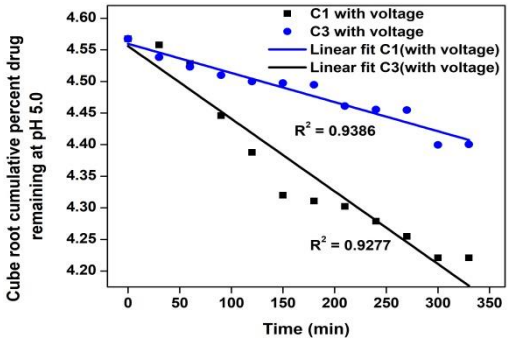
5.4.2.2. Drug release with external electrical signal-

(i) Release at pH 1.5



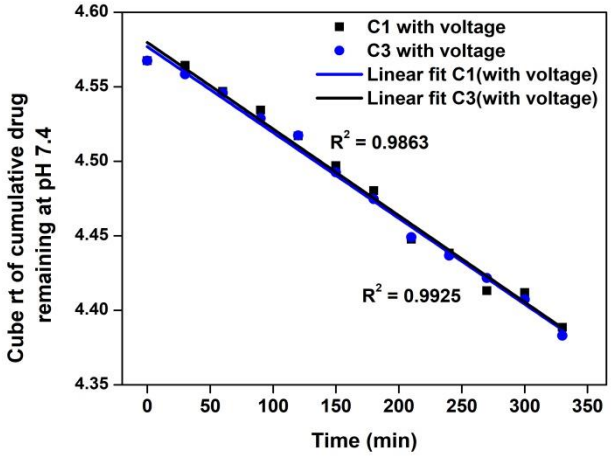
(a)

(ii) Release at pH 5.0



(b)

(iii)Release at pH7.4



(c)

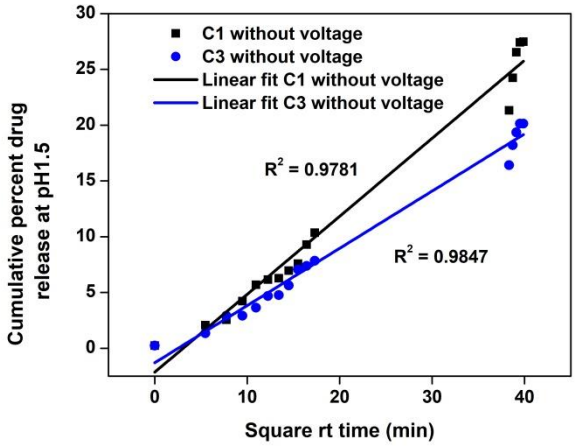
Fig.5.16. Hixson-Crowell drug release with electrical signaling at (a) pH1.5 (b) pH5.0 (c) pH7.4

When the drug release is due to electrical signal, pH 7.4 is best fitted for this model.

5.4.3. Higuchi Model drug release- By using this model dissolution of drug from dosage forms like matrix tablet with water soluble drugs are studied by maintaining perfect sink condition in the release environment. Data obtained were plotted as cumulative percentage of drug release from the hydrogel matrix with square root of time.

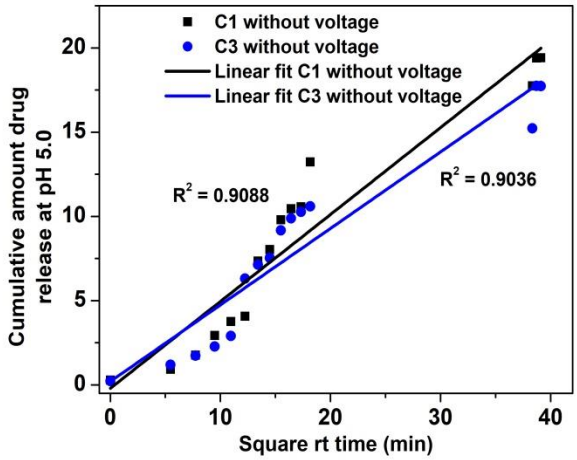
5.4.3.1. Drug release without voltage-

(i) Release at pH 1.5



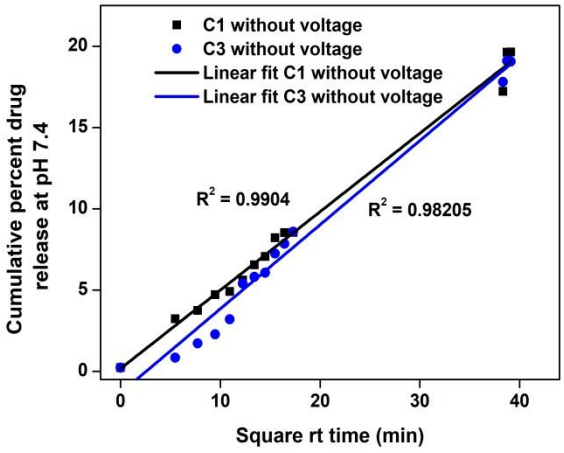
(a)

(ii) Release at pH 5.0



(b)

(iii) Release at pH 7.4



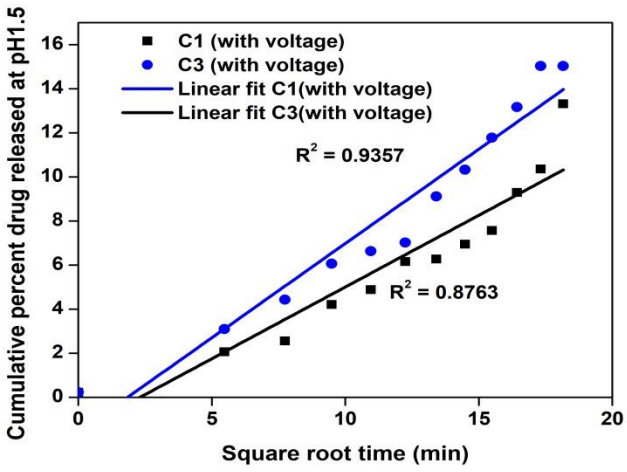
(c)

Fig.5.17. Higuchi drug release without voltage at (a) pH1.5 (b) pH5.0 (c) pH7.4

Both pH 7.4 and 1.5 are both equally suited to this model of drug release profile.

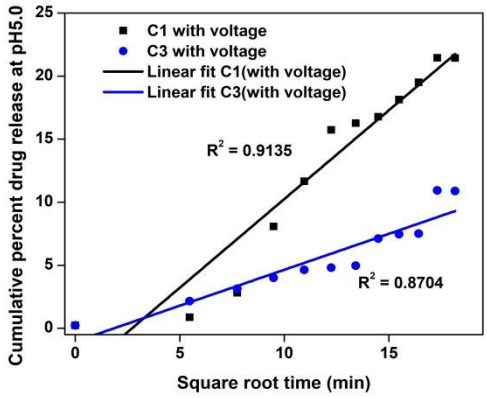
5.4.3.2. Drug Release with external electrical signal

(i) Release at pH1.5



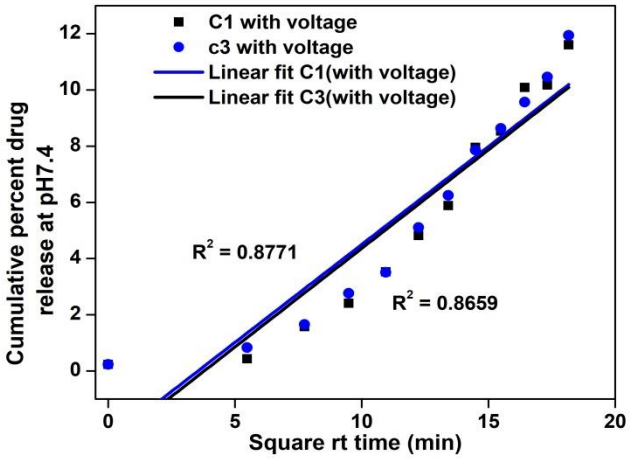
(a)

(ii) Release at pH5.0



(b)

(iii) Release at pH 7.4



(c)

Fig.5.18. Higuchi drug release with electrical signaling at (a) pH1.5 (b) pH5.0 (c) pH7.4

pH 1.5 is the best fit for this model when the system is supplied with external electrical signaling for drug release.

Drug release profiles without electrical stimuli are best fitted with Higuchi model.

Table5.1 R^2 values at pH 1.5 with electrical stimulation

Hydrogel	Zero order	First order	Hixson-Crowell	Higuchi
C1	0.9649	0.9526	0.9526	0.9357
C3	0.9841	0.9838	0.9835	0.8763

Table5.2 R^2 values at pH 5.0 with electrical stimulation

Hydrogel	Zero order	First order	Hixson-Crowell	Higuchi
C1	0.9263	0.9319	0.9277	0.9135
C3	0.9841	0.9373	0.9386	0.8704

Table5.3 R^2 values at pH 7.4 with electrical stimulation

Hydrogel	Zero order	First order	Hixson-Crowell	Higuchi
C1	0.9882	0.9859	0.9863	0.8659
C3	0.9179	0.9921	0.9925	0.8771

Table5.4 R^2 values at pH 1.5 without electrical stimulation

Hydrogel	Zero order	First order	Hixson- Crowell	Higuchi
C1	0.9359	0.9711	0.9702	0.9781
C3	0.9765	0.9701	0.9686	0.9847

Table5.5 R^2 values at pH 5.0 without electrical stimulation

Hydrogel	Zero order	First order	Hixson-Crowell	Higuchi
C1	0.9243	0.7934	0.8013	0.9088
C3	0.9463	0.8089	0.7861	0.9036

Table5.6 R^2 values at pH 7.4 without electrical stimulation

Hydrogel	Zero order	First order	Hixson-Crowell	Higuchi
C1	0.9222	0.9459	0.9424	0.9904
C3	0.9733	0.9436	0.9394	0.98205

Chapter 6:

Conclusion

- Hydrogel incorporated with polypyrrole as the conducting polymer was developed which enabled the invitro electrochemical release of Chlorpromazine loaded inside with and without the aid of external electrical signal.
- The release profile revealed that the maximum amount of drug release was seen at pH 1.5. This is significant because, in case of many disorders due to presence of foreign pathogens or secretions the physiological pH of the localized tissue turns acidic. Such delivery systems can be employed to release the drug locally to areas of acidic pH.
- For the hydrogel without conducting polymer, maximum rate of drug release is achieved at pH7.4.
- In case of hydrogel without conducting polymer, the rate of drug release remains almost unaffected upon electrical stimuli for pH 5.0 and 7.4. But for pH 1.5, drug release rate is almost twice enhanced upon applying electrical stimuli.
- In case of CP-hydrogel hybrid system, electrical stimuli enhance the drug release; almost 3times at pH 1.5, two times at pH 5.0 and slightly less than two times for pH 7.4.
- However with electrical stimulation, the percentage enhancement of rate of release becomes maximized at the lowest pH value of 1.5.
- Therefore, use of PPy enables one to enhance rate of drug release with electrical stimuli and thus enables shifting of pH sensitivity: maximum drug release occurs at acidic pH which is in contrary to the maximum release through hydrogel in the slightly alkaline condition.
- Also, on comparing the release data obtained with only diffusion to those under electrical stimulus, it is seen that the amount of drug released is more in case of electrical stimulus.
- Higuchi model is best fitted for drug release without electrical signaling.
- Drug release from the polymer matrix by electrical stimulation follows linear order characteristics at any pH.

This system can be potentially engineered to be used as an injectable implant and hence the side-effects of the conventional method of drug administration prescribed for psychotic ailments can be substantially lowered.

Reference

[1] Lorenzo, C. A., Fernandez, B. B., Puga, A. M., & Concheiro, A. (2013). Advanced Drug Delivery Reviews. 23: 345-356. Crosslinked ionic polysaccharides for stimuli-sensitive drug delivery.,

[2] Wiley, Devin.: (2013) Proc Natl Acad Sci U S A. **110** (21)8662–7.Transcytosis and brain uptake of transferrin-containing nanoparticles by tuning avidity to transferrin receptor. "[3] Howard C. Ansel, NIcholos G. Popvich, lyold V. Allen , pharmaceutical dosage forms and Drug Delivery system.

[4] J. Siepmann,(2001) advanced drug delivery reviews, 48: 139-157. Modeling of drug release from delivery system based on hydroxypropyl methylcellulose (HPMC),

[5] G. G. Wallace, (1997) Technomic Pub. Co., Lancaster, PA,52:212-218.Conductive Electroactive Polymers: Intelligent Material Systems,.

[6] Y. Lin, G.G. Wallace, (1994) J. Control. Release, 30 137–142. Factors influencing electrochemical release of 2, 6-anthraquinone disulphonic acid from polypyrrole,

[7]. C. E. Schmidt, V. R. Shastri, J. P. Vacanti and R. Langer,(1997) Proceedings of the National Academy of Sciences of the United States of America 94 (17) 8948-8953. Stimulation of neurite outgrowth using an electrically conducting polymer..

[8] P. M. George, A. W. Lyckman, D. A. LaVan, A. Hegde, Y. Leung, R. Avasare, C. Testa, P. M. Alexander, R. Langer and M. Sur,(2005) Biomaterials **26** (17) 3511-3519.
Fabrication and biocompatibility of polypyrrole implants suitable for neural prosthetics,

[9] T. Aoki, M. Tanino, K. Sanui, N. Ogata, K. Kumakura, T. Okano, Y. Sakurai and M. Watanabe, (1995) Synthetic Metals 71 (1-3) 2229-2230. Culture of Mammalian-Cells on Polypyrrole-Coated Ito as a Biocompatible Electrode.

[10] J. Y. Wong, R. Langer and D. E. Ingber (1994) Proceedings of the National Academy of Sciences of the United States of America 91 (8) 3201-3204. Electrically Conducting Polymers Can Noninvasively Control the Shape and Growth of Mammalian-Cells.

[11] A. B. Smith, Knowles, C.J., 9(1990 Biotechnol. Appl. Biochem 12 (6) 661-669. Potential Role of a Conducting Polymer in Biochemistry - Protein Binding Properties.

[12] B. Zinger, L.L. Miller (1984) J. Am. Chem. Soc. 106 6861. Timed release of chemicals from polypyrrole films.

[13] Yuksel N, (2000) , Int. J Pharm; 209: 57-64 Comparison of in vitro dissolution profile by ANONA- based, model – dependent and independent methods.

[14] M.Hepel,F.Mahdevi, Microchem.J.56(1997)54 Application of the Electrochemical Quartz Crystal Microbalance for Electrochemically Controlled Binding and Release of Chlorpromazine from Conductive Polymer Matrix.

[15] Hacker MC, Mikos AG (2011) 2nd ed.; p. 587–622. Synthetic polymers, principles of regenerative medicine.

[16] Shi Qiu, ke wang, (2014) dx,doi/10.14227/DT210214p6. *In vitro* dissolution studies of immediate release and extended-Release formulation using flow through cell apparatus4 , dissolution technologies.

[17] Lachman, L.; Lieberman, H. A.; Kanig J.L. Eds.(1991) p.346-373; Theory and Practice of Industrial Pharmacy. 3rd ed Philadelphia.

[18] Ahuja N. (2007) Eur.J.Pharm and Biopharm, 65: 26-36, Studies on dissolution enhancement and mathematical modelling of drug release of a poorly water soluble drug using water soluble carriers.

[19] M. Pyo, G. Maeder, R.T. Kennedy, J.R. Reynolds, J. Electroanal. Chem. 368 (1994)329

[20] D.D. Ateh, H.A. Navsaria, P. Vadgama,(2006) J. R. Soc. Interface 3, 741–752. Polypyrrole-based conducting polymers and interactions with biological tissues..

[21] Paulo Costa,(2001) European journal of Pharmaceutical sciences, 13: 123-133. Modeling and comparison of dissolution profile,

[22] Van der Linden, H.J.; Herber, S.; Olthuis, W.; Bergveld, P.; *Analyst* 2003, *128*, 325.

[23] Kim, B.C.; Spinks, G.M.; Wallace, G.G.; John, R.; *Polymer* (2000) , 41, 1783.

[24] Mahde Basam, Radia D. Nadher, Jamel O. Hayder. (2018) Journal of pharmaceutical Science and research. Synthesis and characterization of polyacrylamide hydrogel for the controlled release of aspirin.

[25] Maolin Z, Jun L, Min Y, Hongfei H. (2000) Radiat Phys Chem ;58:397–400. The swelling behaviour of radiation prepared semi-interpenetrating polymer networks composed of polyNIPAAm and hydrophilic polymers.

[26] Takashi L, Hatsumi T, Makoto M, Takashi I, Takehiko G, Shuji S. Synthesis of porous poly(N-isopropylacrylamide) gel beads by sedimentation polymerization and the morphology. J Appl Polym Sci 2007;104(2):842.

[27] Yang L, Chu JS, Fix JA. Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation. Int J Pharm 2002;235:1–15.

[28]. Gautam Singhavi, (2011) Review: *In vitro* drug release characterization models, Internationaljournal of Pharmaceutical studies and research; 2: 77-84.

[29] Hussain Lokhandwala, Kinetic modeling and dissolution profiles comparison: An overview, Int.J.Pharm Bio Sci., January 2013; 4(1): 728-737.

[30] J. Siepmann, Modeling of drug release from delivery system based on hydroxypropyl methylcellulose (HPMC), advanced drug delivery reviews, (2001); 48: 139-157.

[31] Suvakanta Dash, Kinetic modeling on drug release from controlled drug delivery system,Acta Polonia Pharmaceutical-drug research, 2010; 67: 217-223.

[32] Masayuki Yokoyama, Glenn S. Kwon, Teruo Okano, Yasuhisa Sakurai, Takashi Seto,f and Kazunori Kataoka. Bioconjugate Chem. 1992, 3, 295-301 295.Preparation of Micelle-Forming Polymer-Drug Conjugates.

[33] Shasha Honga, Zengbo Li a, Chenzhong Li b, Chuan Donga, Shaomin Shuanga. Applied surface Science.Volume 427,PartB,(2018)1189-1198 Cyclodextrin grafted polypyrrole magnetic nanocomposites toward the targeted delivery and controlled release of doxorubicin.

[34] Kyo¨sti Kontturi, Pa¨ivi Pentti, Go¨ran Sundholm .Journal of Electroanalytical Chemistry 453 (1998) 231–238. Polypyrrole as a model membrane for drug delivery.

[35] Kashma Sharma a , Vijay Kumar a, * , Babulal Chaudhary b , B.S. Kaith c , Susheel Kalia d , H.C. Swart .Polymer Degradation and Stability 124(2016) 101-111. Application of biodegradable superabsorbent hydrogel composite based on Gum ghatti-co-poly(acrylic acid-aniline) for controlled drug delivery.

[36] Kyo¨sti Kontturi, Pa¨ivi Pentti, Go¨ran Sundholm .Journal of Electroanalytical Chemistry 453 (1998) 231–238.Polypyrrole as a model membrane for drug delivery.

[37] Suparna Saha, Priyabrata Sarkar, Mrinmoy Sarkar, Biplab Giri. Royal Society of Chemistry Advances 5, (2015) 27665.Electroconductive smart polyacrylamide–polypyrrole (PAC–PPY) hydrogel: a device for controlled release of risperidone.

[38] Richard Justin, Biqiong Chen. Carbohydrate polymers 103(2013)70-80.Characterisation and drug release performance of biodegradablechitosan–graphene oxide nanocomposites.

[39] Zhou, C., & Wu, Q. (2011). A novel polyacrylamide nanocomposite hydrogel reinforced with natural chitosan nanofibers. Colloids and Surfaces B: Biointerfaces,84, 155–162.

[40]. Xie, C. X., Feng, Y. J., Cao, W. P., Teng, H. K., Li, J. F., & Lu, Z. Y. (2009). Novel biodegradable flocculating agents prepared by grafting polyacrylamide to konjac. Journal of Applied Polymer Science, 111, 2527–2536.

[41] Mandal, S., Basu, S. K., & Sa, B. (2010). Ca2+ ion cross-linked interpenetrating network matrix tablets of polyacrylamide-grafted-sodium alginate and sodium alginate for sustained release of diltiazem hydrochloride. Carbohydrate Polymers, 82, 867–873.

[42] Chhatbar et al., 2009; Dong, Dong, Cao, Han, Ding, (2011) Carbohydrate Polymers. 76,650-656.Microwave assisted rapid method for hydrolysis of sodium alginate for M/G ratio determination.

[43] Mandal, B., Ray, S. K., & Bhattacharyya, R. (2012) Journal of Applied Polymer Science, 124, 2250–2268. . Synthesis of full and semi interpenetrating hydrogel from polyvinyl alcohol and poly (acrylic acid-cohydroxyethylmethacrylate) copolymer: Study of swelling behavior, network parameters, and dye uptake properties.

[44] Pongjanyakul, Priprem, Puttipatkhachorn,(2005) Journal of Controlled Release,107. 343-356. Investigation of novel- alginate magnesium aluminium silica microcomposite films for modified-release tablets.

[45] Pereira, R., Carvalho, A., Vaz, D. C., Gil, M. H., Mendesa, A., & Bartolo, P. (2013) International Journal of Biological Macromolecules, 52, 221–230. Development of novel alginate based hydrogel films for wound healing Applications.

[46] Sand, A., Yadav, M., Mishra, D. K., & Behari, K. (2010) Carbohydrate Polymers, 80, 1147–1154. Modification of alginate by grafting of N-vinyl-2-pyrrolidone and studies of physicochemical properties in terms of swelling capacity, metal-ion uptake and flocculation..

[47] Solpan, D., Torun, M., & Guven, O. (2008). The usability of (sodium alginate/ acrylamide) semi-interpenetrating polymer networks on removal of some textile dyes. Journal of Applied Polymer Science, 108, 3787–3795.

[48] Lutfi Genç, Hadi Bilaç and Erden Güler (1998). International Journal of Pharmaceutics,169,232-235. Preparation of controlled release dosage forms of diphenhydramine was prepared with different polymers.

[49] X. Luo, X.T. Cui (2009) Electrochem. Commun.11. 1956–1959, Sponge-like nanostructured conducting polymers for electrically controlled drug release.

[50] George, P. M.; LaVan, D. A.; Burdick, J. A.; Chen, C.-Y.; Liang, E.; Langer(2006) R. Adv. Mater.18, 577–581.Electrically Controlled Drug Delivery from Biotin-Doped Conductive Polypyrrole.

****